Estimating Vitamin D status and the choice of supplementation dose-reply

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LESS IS MORE

Estimating Vitamin D Status and the Choice of Supplementation Dose

To the Editor In a recent issue of *JAMA Internal Medicine*, Bischoff-Ferrari and colleagues[1] reported the results of an interesting randomized clinical trial testing the efficiency of physiological (equivalence, 800 IU/d) and supraphysiological doses (equivalence, 2000 IU/d or 800 IU/d plus calcifediol 300 µg/mo) of vitamin D supplements in lowering the risk of functional decline. The authors found that older participants in the higher-dose vitamin D groups experienced the greater incidence of falls,[1] a result already described with mega doses of vitamin D supplementation[2] but in contradiction with the well-recognized antifall effect of physiological doses.[3]

Before claiming that high-dose vitamin D supplementation makes seniors fall, we wish to draw attention to the secondary analyses stratified by initial vitamin D status.[1] The 12-month number of falls was greater after high-dose vs low-dose vitamin D supplementation only in the group that had no hypovitaminosis D at baseline (ie, 25-hydroxyvitamin D [25(OH)D] ≥ 20 ng/mL [to convert 25[OH]D level to nanomoles per liter, multiply by 2.496]), but not in the group with initial hypovitaminosis D less than 20ng/mL (P = .03 and P = .33, respectively). It thus appears that, among people without hypovitaminosis D, high-dose vitamin D supplementation, aimed at increasing 25(OH)D concentration to supraphysiological levels, is probably not useful—and might be toxic—compared with lower doses aiming at preventing hypovitaminosis D and maintaining 25(OH)D concentration to physiological levels.

These data confirm the current hypothesis of a possible U-shaped or J-shaped effect of vitamin D, with both low and high 25(OH)D concentrations being associated with adverse health events.[4] For this reason, we call for the need to determine older individuals' vitamin D status before any vitamin D supplementation. However, we recognize that such systematic screening for hypovitaminosis D is currently compromised in this population due to the cost of 25(OH)D assay, which is higher than the annual supplementation. To avoid the current trend toward universal supplementation on sight, and to help determining which individuals should receive lower-dose or higher-dose vitamin D supplements, it is urgently needed to develop new cost-effective routine screening strategies to provide an appropriate medical decision. For instance, we recently developed a clinical tool able to identify older adults with hypovitaminosis D who may be administered high-dose supplements without blood test.[5] Further investigations will be necessary to examine the feasibility, cost-effectiveness, and usefulness of such tools in daily practice and to estimate if they allow supplementing older adults in a personalized way, thus avoiding vitamin D toxic effects described by Bischoff-Ferrari and colleagues.

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Conflict of Interest Disclosures: None reported.

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In Reply We agree that high-dose monthly vitamin D is not necessarily harmful among seniors with vitamin D deficiency. However, everyone treated with 24 000 IU vitamin D per month (equivalent to 800 IU/day) achieved the replete range of above 20 ng/mL 25(OH)D (to convert 25[OH]D level to nanomoles per liter, multiply by 2.496), with none reaching a 25(OH)D level above 45 ng/mL.[1] The group treated with 24 000 IU per month included 59.7% of participants with deficient 25(OH)D starting levels less than 20 ng/mL and 40.3% with replete 25(OH)D starting levels greater than 20 ng/mL (range, 20.1-43.5 ng/mL). Thus, at starting levels throughout the wide range of 4.9 to 43.5 ng/mL, 24 000 IU vitamin D per month appears to be effective in safely bringing 25(OH)D levels into what currently appears to be the desirable range for fall prevention.[1] This does not mean that measuring 25(OH)D status is never indicated but suggests that wide spread assessments by serum analysis or algorithm may not be necessary.

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Adverse Effects of Proton Pump Inhibitors in Chronic Kidney Disease

To the Editor Proton pump inhibitors (PPIs) are extensively used for common gastrointestinal disorders where the inhibition of gastric acid secretion is desirable, such as gastroduodenal ulcer, dyspepsia and gastroesophageal reflux disease. Lazarus et al[1] showed an association between PPI use and a higher risk of incident chronic kidney disease (CKD). Furthermore, the authors touched on PPI induced hypomagnesemia as a possible mediator of CKD worsening. We agree with and support this hypothesis, expanding on the possible adverse effects of inappropriately prescribed PPIs in patients with CKD. Proton pump inhibitors interfere with the active transport of magnesium, and clinically significant phenomena are observed in the carriers of heterozygotic mutations of TRPM6/7.[2] Proton pump inhibitor-associated hypomagnesemia has been highlighted both in the general population and patients with CKD. We showed that chronic PPI use is associated with increased vascular calcification risk in hemodialysis patients.[3] Because magnesium is acting as inhibitor of calcification, it is possible that PPI-induced hypomagnesemia may worsen vascular calcifications in patients with CKD. Magnesium is also deposited in large quantities in bone, being essential for bone health, and chronic PPI treatment may be associated with clinical spine, forearm or wrist, and total fractures, although not hip fractures and with only a marginal effect on 3-year bone mineral density change at the hip.[4]

There is another potential mechanism justifying the increased risk of CKD progression observed by Lazarus et al.[1] Proton pump inhibitor administration increased plasma asymmetric dimethylarginine (ADMA) levels and reduced nitric oxide levels and endothelium-dependent vasodilation in a murine model and ex vivo in human tissues. Proton pump inhibitors increased ADMA because they bind to and inhibit dimethylarginine dimethylaminohydrolase, the ADMA catabolic enzyme. This observation offers a plausible biological mechanism to explain the observed association of PPI treatment with increased major adverse cardiovascular events in patients with acute coronary syndrome,[5] but ADMA elevation may also have a relevant effect on CKD progression. We suggest that prescription of PPIs for patients with CKD, heavily exposed to the risk of cardiovascular morbidity and mortality, should be carefully considered because of their possible adverse effects on cardiovascular health and bone health. Proton pump inhibitors are potentially inappropriate medications in CKD patients.

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To the Editor In an investigation to quantify the association between the use of proton pump inhibitors (PPIs) and incidence of chronic kidney disease (CKD) in a population-based cohort, Lazarus et al[1] concluded that PPI use is associated with a higher risk of CKD. In this sense, we would like to express concern about the baseline characteristics of patients who are prescribed PPIs that could constitute an important source of bias. Indeed, PPI users were more likely than nonusers to have a greater burden of prescribed medications and comorbidities that influence the baseline risk of CKD for reasons unrelated to their PPI use.

In fact, there is supportive evidence that nonsteroidal anti-inflammatory drug (NSAID) use is associated with increased risk of CKD in patients with hypertension,[2] and a triple therapy combination of diuretics with angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers and NSAIDs was associated with an increased risk of acute kidney injury.[3] Moreover, the coexistence of hypertension is associated with more rapid progression of CKD,[4] and CKD is frequently the result of hypertension and diabetes mellitus.[5]

Thus, under circumstances like the raised and combined presence of several risk factors (eg, NSAID and ACE inhibitor use, diagnosis of hypertension, diabetes mellitus) that increase the risk of CKD among PPI users at baseline, the selection of patients could be biased making the interpretation of hazard ratio data very difficult in spite of the stratification because the underlying hazard function would be different among PPI users and patients who do not use PPIs.

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